IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Rosen et al.	
Application No.: 09/960,665	
Filed: 9/21/2001	Group Art Unit: 1624
Title: Methods and Compositions for Degradation and/or Inhibition of HER Family Tyrosine Kinases	Examiner: B. Kifle
	Conf. Number: 5586
Attorney Docket No.: MSK.P-038-2	

BRIEF FOR APPELLANT

This brief is filed in support of Applicants' Appeal from the final rejection mailed 5/21/2003. Consideration of the application and reversal of the rejections are respectfully urged.

Real Party in Interest

The real party in interest is the assignee Sloan-Kettering Institute for Cancer Research. The application is licensed to Conforma Therapeutics Corporation.

Related Appeals and Interferences

A Notice of Appeal was filed on October 10, 2003 in the parent case, Serial No. 09/937,192.

Status of Claims

I hereby certify that this paper and any attachments named herein are being deposited with the US Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on 22 Oct 03.

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22 Oct 03

Date of Signature

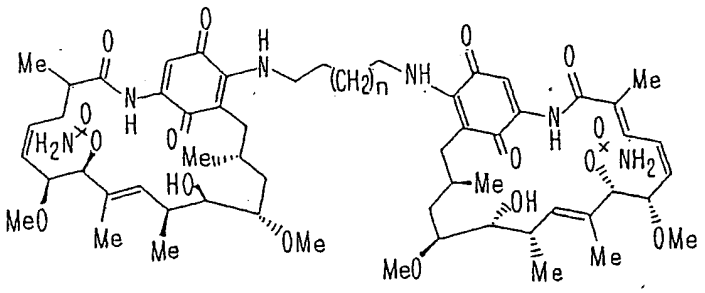
Claims 1-40 are pending in this application. Claims 1, 2, 6, 7, 12, 13 and 15-40 are the subject of this appeal. Claims 3-5 and 8-11 have been cancelled. Claim 14 is being canceled in an amendment filed after Appeal, as it is duplicative with claim 36.

Status of Amendments

All amendments prior to Appeal have been entered. An Amendment After Appeal is being filed to cancel claim 14. Inasmuch as entry of this amendment is anticipated, this amendment and all prior amendment are reflected in the Appendix listing the Claims on Appeal.

Summary of Invention

The claims of this application relate to bifunctional molecules comprising two linked heat shock protein (hsp-binding moieties which bind to hsp90 in the pocket to which ansamycin antibiotics bind. These bifunctional molecules are effective for inducing the degradation and/or inhibition of proteins, including HER-family tyrosine kinases in the cells with which they interact. For example, a composition having the structure



*Dimers: n = 4

provides selective degradation and/or inhibition of HER-family tyrosine kinases, without substantially affecting other kinases. Thus, the compositions of the invention can be used for treatment of HER-positive cancers with reduced toxicity, since these compounds potently kill cancer cells but affect fewer proteins than geldanamycin, an ansamycin antibiotic, when used by itself. This activity of hsp-binding compounds is not limited to to HER-kinase. Thus, the

compositions of the invention can be used theraeutically against a broad range of cancers expressing other proteins degraded in the presence of hsp90 binding molecules.

In the pending claims, claims 1, 2, 6, 7 and 18-25 are directed to bifunctional chemical compounds. Claims 12 and 26-30 are directed to a method for destruction of cells expressing a HER-family kinase using a compound of the type set forth in the composition claims. Claims 13 and 31-40 are directed to a method for treating cancer. Of these claims 36-40 are directed to treating cancers expressing a HER-family kinase.

Issues on Appeal

(1) Whether claims 1, 2, 6, 7 and 12-40 meet the definiteness requirements of 35 USC § 112, second paragraph?

(2) Whether claims 13-17 and 31-36 are enabled by the teaching in the specification?

Applicants submit that both of these issues should be answered in the affirmative, and the rejection of the claims reversed in full.

Grouping of Claims

Claims 1, 2, 6, 7 and 12-40 are rejected as indefinite for three different reasons. These reasons are not all applicable to all of the rejected claims. Accordingly:

(a) the claims are all argued as a single group with respect to the first ground for the indefiniteness rejection and stand or fall together;

(b) claims 6, 16-29, and 31-33 are argued separately from claims 1, 2, 7, 12-15, 30, and 34-40 with respect to the second ground for rejection and these groups of claims do not stand or fall together; and

(c) claims 12 and 26-30 are argued as a group with respect to the third ground for rejection which is not applicable to the other claims.

Claims 13, 15-17 and 31-36 are rejected for lack of enablement. Claims 13, 15-17 and 31-35 are argued as one group with respect to this rejection. Claim 36, which recites

treatment of a cancer expressing a HER-family kinase is argued as a second group with respect to this rejection. These two groups do not stand or fall together.

Argument

The Indefiniteness Rejection

Claims 1, 2, 6, 7 and 12-40 stand rejected under 35 USC § 112, second paragraph, as indefinite and the Examiner has offered three reasons for this rejection. These reasons, as set forth in the Advisory Action are:

(1) an alleged ambiguity because "it is still unclear where on the geldanamycins the linker is bonded;"

(2) an alleged ambiguity because "the nature of the linker is not known;" and

(3) in claims 12 and 26-30, an alleged ambiguity because "it is unclear where these cells are that are to be destroyed.

For the reasons set forth below, Applicants submit that all of these reasons are in error.

35 USC § 112, second paragraph, creates a requirement that an Applicant must present claims "particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.," The "essence of that requirement is that the language of the claims must make it clear what subject matter they encompass." *In re Hammack*, 166 USPQ 204 (CCPA 1970). This requirement has usually been viewed from the perspective of a potential infringer, "so that they may more readily and accurately determine the boundaries of protection involved and evaluate the possibility of infringement and dominance." 166 USPQ at 208.

In order to support a rejection under 35 USC § 112, it is the Examiner's burden to state why a person skilled in the art would be unable to understand the scope of the claim when it is read in light of the specification. *Ex Parte Cordova*, 10 U.S.P.Q. 2d 1949, 1952 (POBAI 1989). This burden is not met merely by stating that the claim may encompass several different embodiments, in the absence of any argument or reasoning that such a scope is inconsistent. The Examiner is required to present reasons as to why a person skilled in the art would be unable to

understand the scope of the claims when read in light of the specification. Stated differently, the mere fact that a claim may be broad such that it encompasses several embodiments is not a basis to reject that claim as indefinite. *In re Skoll*, 187 U.S.P.Q. 481 (C.C.P.A. 1975)(claim reciting organic and inorganic acids found to be broad, not indefinite). The Examiner has not met the burdens in this case, nor established a sound rejection under § 112, second paragraph.

Looking at the first ground for rejection, the Examiner asserts that the claims are indefinite because it is unclear where on the geldanamycin (or in the generic sense on the hsp-binding moiety) the linker is bonded. Claim 1 is representative of the language in the claims to which the Examiner directs the rejection and is reproduced here for convenience:

> 1. A chemical compound comprising first and second hsp-binding moieties which bind to the pocket of hsp90 with which ansamycin antibiotics bind, said binding moieties being connected to one another by a linker.

The concept of a linker, that is a bridging moiety between two active or functional parts of a compound is routine in chemistry. As explained in the specification (Page 4 lines 14-19 and Fig. 1), the linker in the present case is entirely consistent with this common understanding.

> The two hsp-binding moieties are joined by a linker. As discussed in more detail below, this linker may be of varying lengths. Altering the length of the linker results in different activity levels and specificity profiles. In general, the linker will be 1 to 9 carbon atoms in length, and may be a linear carbon chain or a substituted carbon chain, for example incorporating double or triple bonds, an aryl group or a secondary or tertiary amine. (See. Fig. 1)

The Examiner states in the first reason for the rejection, however, that the claims are indefinite because it is not clear where the linker is bound. As has been explained to the Examiner to no avail, however, the claims are not limited to, and are not intended to be limited to specific binding sites. This breadth does not make the claims indefinite.

Furthermore, as a practical matter, since the independent claims are generic with respect to the hsp-binding moiety, there is no reasonable way to indicate the binding location of the linker. One cannot use position numbers, since these will vary with the hsp-binding moiety. Similarly, one cannot identify specific atoms (for example a heteroatom) since these may not always be present. Thus, while persons skilled in the art will appreciate that some positions on

a given hsp-binding moiety are far more easily modified than others, the claims are not indefinite, because a person skilled in the art can surely determine if a linker is present and if it connects the two hsp-binding moieties.

The second ground for rejection is the Examiner's assertion that there is ambiguity because "the nature of the linker is not known." Again, this appears to be a challenge based on breadth of the claims rather than an assertion that a person skilled in the art would be unable to determine if a linker was present. As such, the Examiner as failed to meet his burden to show that a person skilled in the art would not understand the scope. Furthermore, claims 6, 16-29, and 31-33 all provide additional limitations concerning the nature of the linker, including very specific limitations such as that the linker is an N-methylamino linker ((Claims 20 and 28). The Examiner has never indicated why this specification of the linker is not distinguishable from the generic term "linker" and has lumped all of the claims together. For example, he has not said why a person skilled in the art would have difficulty identifying a linker that includes an N-methylamino group, or that has a length of 4-7 carbon atoms (as set forth in claims 16) or a linker that is substituted carbon chain incorporating an aryl group (as set forth in claim 21). Thus, it appears that nothing less than a specific listing of the possible linker species will satisfy the Examiner. Such specificity is not required by 35 USC § 112, second paragraph.

The final ground for rejection is applicable only to claims 12 and 26-30 which refer to a method for destruction of cells. The Examiner states that these claims are indefinite because "it is unclear as to where the cells are that are to be destroyed." The Examiner has never provided a reason why the location of the cells is in any way relevant to an understanding of the scope of the claims. Furthermore, the location of the cells does not matter, provided that they can be treated with the chemical compound. In this regard, Applicants note that the examiner has argued that destroying cells in a petri would not accomplish anything (thus raising a specter of a utility rejection). In response, Applicants point out that destroying cancerous cells *ex vivo* (including in a petri dish) may be desirable where material is removed from a patient, treated and later returned to the patient.

In short, the claims mean exactly what they say -- destroying cells. If cells are destroyed, the claim does not distinguish between locations where this is accomplished. As to

the Examiner's assertion in the Official Action of May 21, 2003 that "it is unclear which cells are expressing a HER-family tyrosine kinase and which ones are not", this assertion is still not understood by Applicants, and has not been clarified by the Examiner. The claims are directed to destroying cells that do express the HER-family kinase. To the extent that other cells are present, they are not relevant to the claimed method.

For these reasons, Applicants submit that the rejection of the claims under 35 USC § 112, second paragraph, is in error and should be reversed in its entirety.

The Enablement Rejection

The Examiner has rejected the method claims that do not recite a specific cancer, i.e., claims 13-17 and 31-36, as lacking enablement. These claims are properly considered in two groups, first claims 13 and 31-35 which do not specifically recite that the cancer is one that expresses HER kinase, and claims 36 which does make this recitation, although the Examiner has refused to give separate consideration on this basis.

The basis for the enablement rejection is the Examiner's statement that the claims "are drawn to the treatment of cancer generally," and his unsupported assertion that "no compound has ever been found that can treat cancers generally." The basis for this argument is largely that the Examiner is classing cancer therapy with perpetual motion machines and assumes in assessing enablement that it is inherently unbelievable that a cancer therapy could work generally. Such may have been the case when *In re Buting,* 163 USPQ 689 (CCPA 1969) cited by the Examiner, was decided in 1969, but the art and the law have progressed since then. The notion of automatic unbelievability is no longer credited. Indeed, as the Board of Appeal noted in 1987 in *Ex parte Rubin*, 5 USPQ2d 1461, 1462 (POBAI 1987), "'contemporary knowledge in the art ' has far advanced since the days when the any statement of utility in treating cancer was per se 'incredible.'" Here, the Examiner has not offered any reasoning as to why the assertions of general utility in this application, given the suggested mechanism of action. As such, the Examiner has failed to meet the burden discussed in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971), where it is noted that:

> a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond to those used in describing and defining the subject matter sought to be patents *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112, *unless* there is a reason to doubt the objective truth of the statements contained therein, which must be relied upon for an enabling disclosure.

A over thirty-year-old case, discussing the state of the art at that time, is not a reason to doubt the truth of the asserted utility here.

Furthermore, Applicants have submitted evidence showing that a monomeric ansamycin compound, 17-allylamino-geldanamycin (17-AAG), which is mentioned in the specification on Page 8, line 15 and other hsp90 inhibitors are efficacious in a variety of tumor types including breast cancer, ovarian cancer, pancreatic cancer and gastric cancer (the cancer types specifically mentioned on Page 8, lines 9-11 of the application), other HER kinase overexpressing tumors, and tumors which do not over express HER kinase. For example, Yang et al. (Exhibit A), report inhibition of glioma (brain tumor) cells with 17-AAG. Okabe et al. (Exhibit B) reports *in vivo* activity of herbimycin A (an ansamycin antibiotic) against leukemia cells. Kelland *et al* (Exhibit C, JNCI 91: 1940, 1999) achieved tumor cytostasis in two human colorectal carcinomas, HT29 and BE for the duration of drug treatment with 17-AAG. Burger *et al* (Exhibit D Proc. AACR, 41: Abstract # 2844, 2000) reported potent effects of 17-AAG against a melanoma xenograft and, interestingly, preliminary data from the London arm of the 17-AAG trial indicates that melanoma (2/6 objective responses) may be a responsive tumor (Exhibit E Banerji *et al*, Proc. ASCO, Abstract # 326, 2001) 17-AAG has also been used in studies with prostate cancers, and it has been shown that this administration resulted in dose-dependent inhibition of androgen-dependent and -independent prostate cancer xenografts. (Exhibit F Solit et al., *Clin. Cancer Res.* 8: 986-993, 2002). 17-AAG has also been shown to enhance paclitaxel-mediated cytotoxicity in lung cancer cells (Exhibit G Nguyen et al, *Ann. Thorac. Surg.* 72: 371-379, 2001); and to modulate metastasis phenotypes in non-small cell lung cancer (Exhibit H Nguyen et al., *Ann. Thorac. Surg.* 70: 1853-60, 2000). Thus, the efficacy of compounds that bind to the hsp90 receptor span a wide range of unrelated cancers, thereby refuting the Examiner's statement that generalized cancer therapy is inherently unbelievable.

Despite repeated requests, the Examiner has never commented on these articles. Because of this, Applicants are unable to address here any reasons he may have for deeming the articles insufficient. Applicants do note, however, that the fact that the articles are dated after the filing date of this application is not relevant, since tests performed after the filing date can be used to demonstrate the enablement, and the efficacy of that which was disclosed. Furthermore, while the tests described in the articles do not utilize the specific bifunctional compounds used in the present invention, they use monomeric hsp-binding compounds which could be coupled as quasi dimers, and the use of such dimers would be within the scope of the rejected claims. The Examiner has not offered any reasons as to why a person skilled in the art would doubt the utility of these dimers.

Finally, it should be noted that claim 36 does not, contrary to the Examiner's argument, claim treatment of "all cancers generally." It specifically recites cancers expressing a HER-family tyrosine kinase, and the examples in the application specifically relate to and demonstrate degradation of HER-kinase. The Examiner has provided no reason why persons skilled in the art would doubt the statements of utility as they relate to the specific subset of cancer that express HER-kinases.

For these reasons, the rejection for lack of enablement should be reversed.

Conclusion

In light of the foregoing, favorable consideration of the application and reversal of the rejections of record are respectfully urged.

Respectfully submitted,

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APPENDIX
CLAIMS ON APPEAL

1. A chemical compound comprising first and second hsp-binding moieties which bind to the pocket of hsp90 with which ansamycin antibiotics bind, said binding moieties being connected to one another by a linker.

2. The chemical compound according to claim 1, wherein the first hsp-binding moiety is an ansamycin antibiotic.

3. canceled

4. canceled

5. canceled

6. The chemical compound of claim 2, wherein the linker has a length of 4 to 7 carbon atoms.

7. The chemical compound of claim 6, wherein the linker has a length of 4 carbon atoms.

8. canceled

9. canceled

10. canceled

11. canceled

12. A method for destruction of cells expressing a HER-family tyrosine kinase, comprising administering to the cells a chemical compound comprising first and second hsp-binding moieties which bind to the pocket of hsp90 with which ansamycin antibiotics bind, said binding moieties being connected to one another by a linker.

13. A method for treating cancer in a patient suffering from cancer, comprising administering to the patient a therapeutic composition comprising a chemical compound comprising first and second hsp-binding moieties which bind to the pocket of hsp90 with which ansamycin antibiotics bind, said binding moieties being connected to one another by a linker.

14. The method of claim 13, wherein the cancer is an HER-positive cancer.

15. The method according to claim 13, wherein at least one of the hsp-binding moieties is an ansamycin antibiotic.

16. The method according to claim 15, wherein the linker has a length of 4 to 7 carbon atoms.

17. The method according to claim 16, wherein the linker has a length of 4 carbon atoms.

18. The chemical compound of claim 1, wherein the linker is a substituted carbon chain.

19. The chemical compound of claim 18, wherein the linker is a substituted carbon chain incorporating a secondary or tertiary amine.

20. The chemical compound of claim 19, wherein the linker is an N-methylamino linker.

21. The chemical compound of claim 18, wherein the linker is a substituted carbon chain incorporating an aryl group.

22. The chemical compound of claim 3, wherein the linker is a substituted carbon chain.

23. The chemical compound of claim 22, wherein the linker is a substituted carbon chain incorporating a secondary or tertiary amine.

24. The chemical compound of claim 23, wherein the linker is an N-methylamino linker.

25. The chemical compound of claim 22, wherein the linker is a substituted carbon chain incorporating an aryl group.

26. The method of claim 12, wherein the linker is a substituted carbon chain.

27. The method of claim 26, wherein the linker is a substituted carbon chain incorporating a secondary or tertiary amine.

28. The method of claim 27, wherein the linker is an N-methylamino linker.

29. The method of claim 27, wherein the first and second hsp-binding moieties are each an ansamycin antibiotic.

30. The method of claim 12, wherein the first and second hsp-binding moieties are each an ansamycin antibiotic.

31. The method of claim 13, wherein the linker is a substituted carbon chain.

32. The method of claim 31, wherein the linker is a substituted carbon chain incorporating a secondary or tertiary amine.

33. The method of claim 32, wherein the linker is an N-methylamino linker.

34. The method of claim 32, wherein the first and second hsp-binding moieties are each an ansamycin antibiotic.

35. The method of claim 13, wherein the first and second hsp-binding moieties are each an ansamycin antibiotic.

36. The method of claim 13, wherein the patient treated suffers from a cancer expressing a HER-family tyrosine kinase.

37. The method of claim 36, wherein the cancer is breast cancer.

38. The method of claim 36, wherein the cancer is ovarian cancer.

39. The method of claim 36, wherein the cancer is pancreatic cancer.

40. The method of claim 36, wherein the cancer is gastric cancer.